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AXS-05 Alzheimer's Disease Agitation Phase 3 Clinical Program

ACCORD-2, ADVANCE-2, and Long-term safety
Phase 3 trial topline results

December 30, 2024

Forward Looking Statements & Safe Harbor

Certain matters discussed in this press release are “forward-looking statements”. The Company may, in some cases, use terms such as “predicts,” “believes,” “potential,” “continue,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should” or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. In particular, the Company’s statements regarding trends and potential future results are examples of such forward-looking statements. The forward-looking statements include risks and uncertainties, including, but not limited to, the continued commercial success of the Company’s Sunosi® and Auvelity® products and the success of the Company’s efforts to obtain any additional indication(s) with respect to solriamfetol and/or AXS-05; the Company’s ability to maintain and expand payer coverage; the success, timing and cost of the Company’s ongoing clinical trials and anticipated clinical trials for the Company’s current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including the Company’s ability to fully fund the Company’s disclosed clinical trials, which assumes no material changes to the Company’s currently projected revenues or expenses), futility analyses and receipt of interim results, which are not necessarily indicative of the final results of the Company’s ongoing clinical trials, and/or data readouts, and the number or type of studies or nature of results necessary to support the filing of a new drug application (“NDA”) for any of the Company’s current product candidates, including statements regarding the ability of the ACCORD and ADVANCE clinical trials to support the filing of an NDA for Alzheimer’s disease agitation; the Company’s ability to fund additional clinical trials to continue the advancement of the Company’s product candidates; the timing of and the Company’s ability to obtain and maintain U.S. Food and Drug Administration (“FDA”) or other regulatory authority approval of, or other action with respect to, the Company’s product candidates, including statements regarding the timing of any NDA submission; whether issues identified by FDA in the complete response letter may impact the potential approvability of the Company’s NDA for AXS-07 for the acute treatment of migraine in adults with or without aura, pursuant to the Company’s special protocol assessment for the MOMENTUM clinical trial; the Company’s ability to successfully defend its intellectual property or obtain the necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company’s research and development programs and collaborations; the success of the Company’s license agreements; the acceptance by the market of the Company’s products and product candidates, if approved; the Company’s anticipated capital requirements, including the amount of capital required for the continued commercialization of Sunosi and Auvelity and for the Company’s commercial launch of its other product candidates, if approved, and the potential impact on the Company’s anticipated cash runway; the Company’s ability to convert sales to recognized revenue and maintain a favorable gross to net sales; unforeseen circumstances or other disruptions to normal business operations arising from or related to domestic political climate, geo-political conflicts or a global pandemic and other factors, including general economic conditions and regulatory developments, not within the Company’s control. The factors discussed herein could cause actual results and developments to be materially different from those expressed in or implied by such statements. The forward-looking statements are made only as of the date of this presentation and the Company undertakes no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstance.

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Agenda

Introduction	**Mark Jacobson, MA** Chief Operating Officer
Phase 3 trial results ACCORD-2, ADVANCE-2, long-term safety trial	**Herriot Tabuteau, MD** Founder and Chief Executive Officer
Alzheimer's disease agitation Disease overview	**Sue Giordano, PhD** Vice President, Medical Affairs
Clinical perspective	**Dr. Jeffrey Cummings, MD, ScD** Vice Chair of Research, UNLV Department of Brain Health
Q&A	**Dr. Jeffrey Cummings, MD, ScD** **Herriot Tabuteau, MD** **Mark Jacobson, MA** **Sue Giordano, PhD**

Develop and deliver
transformative medicines
for the hundreds of millions of people impacted by central nervous system conditions

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Summary of topline results

Robust efficacy demonstrated in third pivotal, placebo-controlled trial

- AXS-05 met the primary endpoint in the ACCORD-2 trial by statistically significantly delaying the time to relapse of Alzheimer's disease (AD) agitation compared to placebo (p=0.001)
  - Met key secondary endpoint compared to placebo (p=0.001; prevention of relapse of AD agitation)
  - Reduced worsening of overall AD severity compared to placebo (p<0.001; CGI-S Alzheimer's disease overall clinical status)
- AXS-05 demonstrated numerically greater improvements on primary and secondary endpoints in the ADVANCE-2 trial

Favorable safety and tolerability profile reinforced by long-term, open-label extension trial

- AXS-05 was well tolerated in controlled and long-term trials
- AXS-05 was not associated with death, increased risk of falls, cognitive decline, or sedation
- Long-term safety trial completed with required number of patients treated for 6 and 12 months

AXS-05 (dextromethorphan-bupropion)

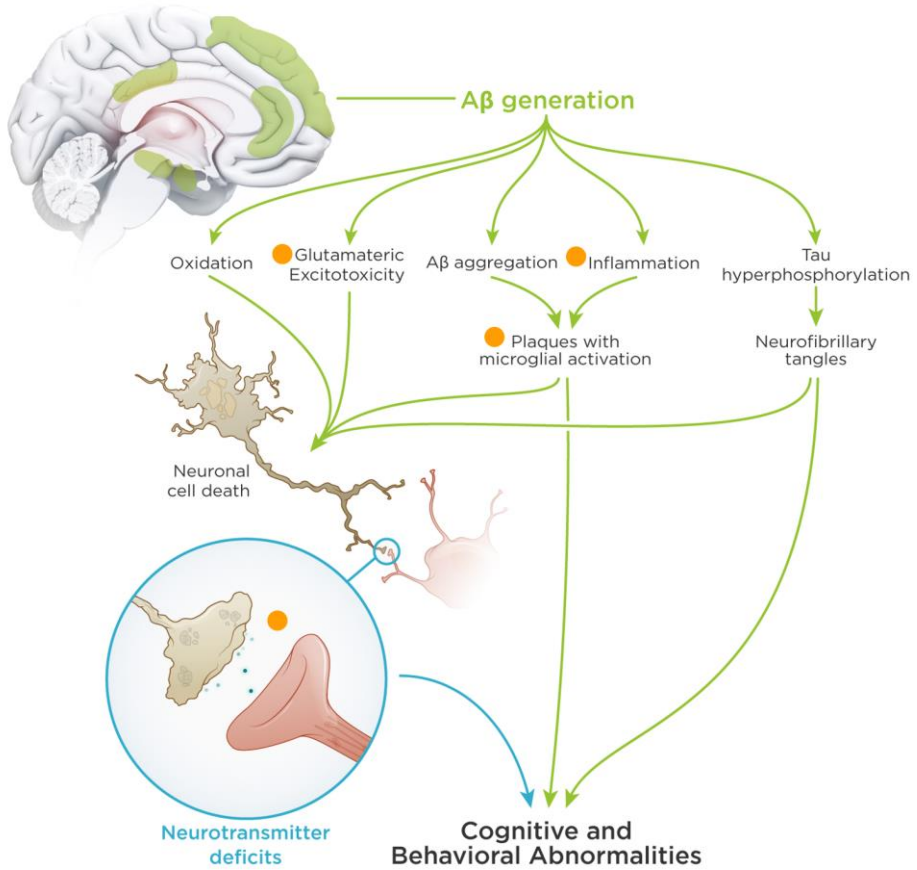
Potentially first-in-class, best-in-class treatment for Alzheimer's disease agitation

In Alzheimer's disease, insoluble Aβ production and accumulation *triggers secondary steps* leading to synaptic loss and neuronal cell death[1,2]

Reductions in certain *neurotransmitters* are thought to contribute to cognitive and behavioral symptoms including agitation and aggression[1-4]

AXS-05 *modulates the function* of neurotransmitters implicated in Alzheimer's disease (glutamate, sigma-1, norepinephrine, and dopamine)[1-4]

Brain regions implicated in AD agitation[4]



AXS-05 pharmacological actions[5,6]

1. Cummings, J.L. *N Engl J Med.* (2004); 2. Querfurth, H.W. & LaFerla, F.M. *N Engl J Med.* (2010); 3. Porsteinsson, A.P. & Antonsdottir, I.M. *Expert Opin Pharmacother.* (2017); 4. Rosenberg, P.B., Nowrangi, M.A., & Lyketsos, C.G. *Mol Aspects Med.* (2015); 5. Stahl, S.M. *CNS Spectr.* (2019); 6. Cheng, W. et al. *Mol Med Rep.* (2015)

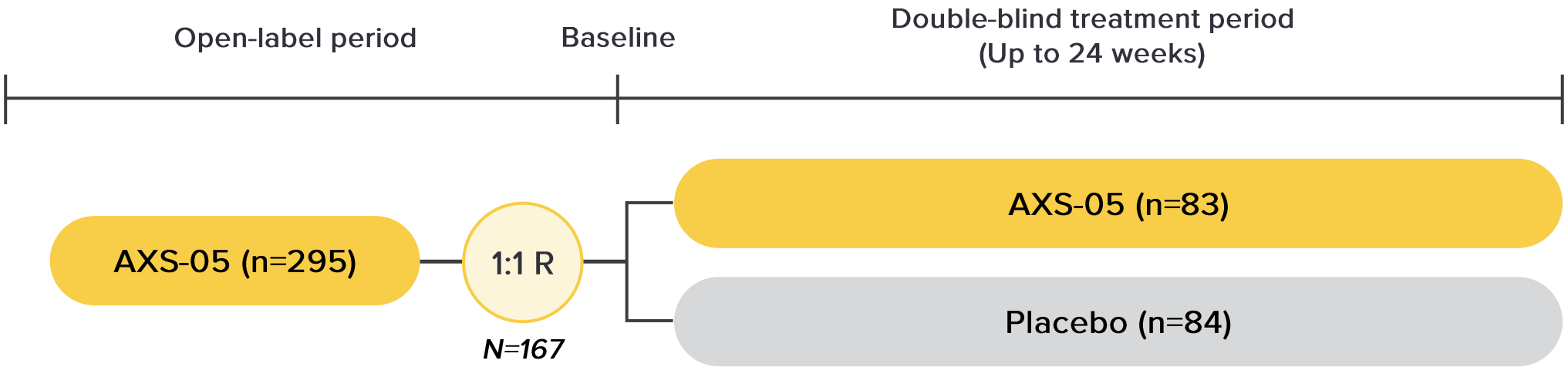
ACCORD-2 Phase 3 trial topline results

ACCORD-1	ADVANCE-1†	ACCORD-2	ADVANCE-2	Long-term safety
Phase 3 (N=108)	*Phase 2/3 (N=366)*	*Phase 3 (N=167)*	*Phase 3 (N=408)*	*Phase 3 (N=456)*
• Efficacy and safety of AXS-05 vs. placebo • 9-week, open-label treatment period followed by 26-week, double-blind, multi-center, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Efficacy and safety of AXS-05 vs. placebo • Open-label treatment period followed by 24-week, double-blind, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Long-term efficacy and safety of AXS-05 • 12-month, open-label extension (OLE) of ACCORD-1 and ADVANCE-2

†Also established component contribution by demonstrating statistical superiority vs. bupropion

ACCORD-2 trial design

Phase 3, multi-center, double-blind, placebo-controlled, randomized withdrawal trial



Key eligibility criteria

- 65-90 years of age
- Diagnosis of probable AD (NIA-AA) and clinically significant agitation resulting from probable AD
- MMSE between 10 and 24
- NPI-AA score ≥4

Primary endpoint

- Time from randomization to relapse of agitation

Relapse criteria

- ≥10-point increase (worsening) from randomization in the CMAI total score
- CMAI total score ≥ baseline CMAI total score
- Hospitalization for worsening AD agitation

AD = Alzheimer's disease; NIA-AA = National Institute on Aging-Alzheimer's Association; MMSE = Mini-Mental State Examination; NPI-AA = Neuropsychiatric Inventory-Agitation/Aggression domain

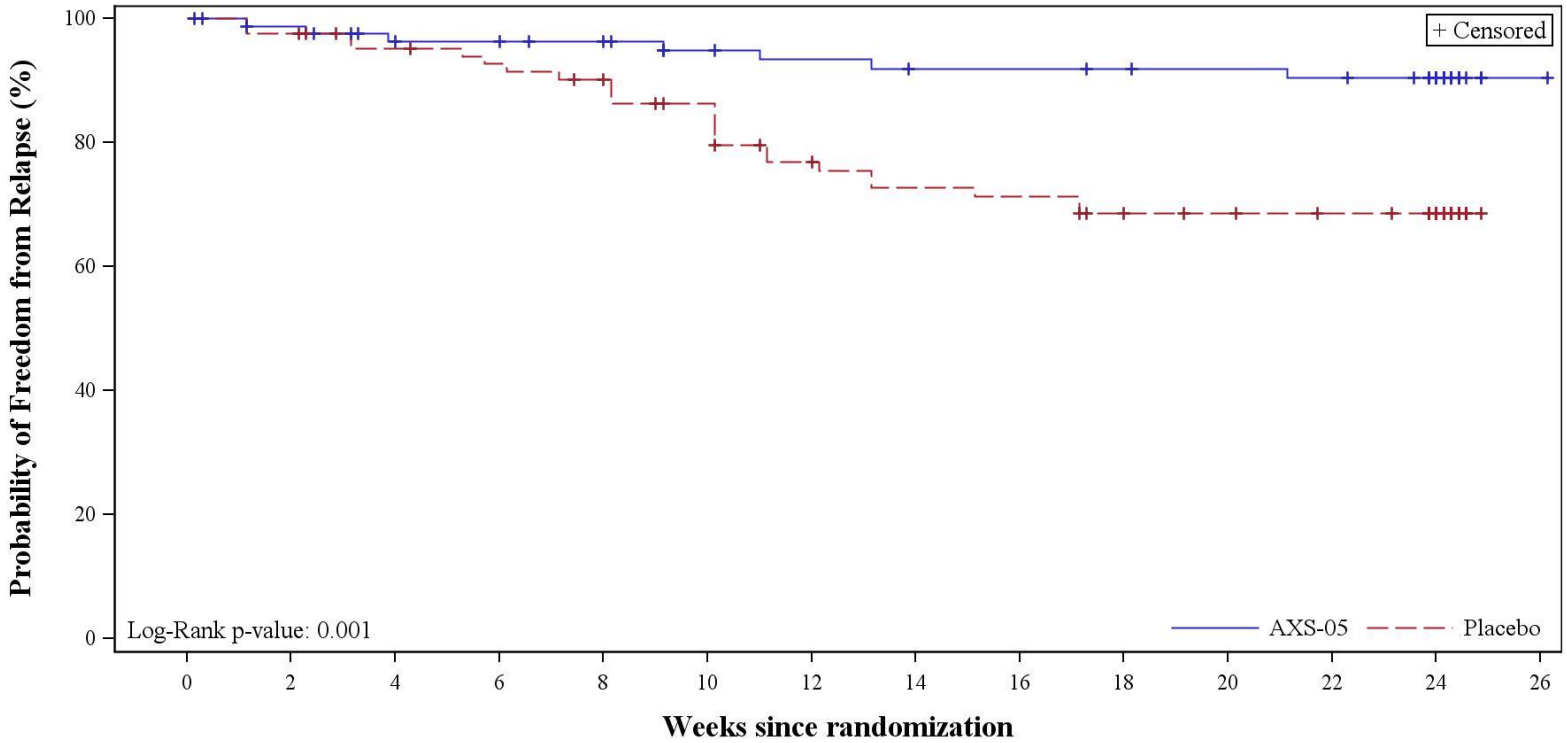
ACCORD-2 demographics and baseline characteristics

	Open-label period	Double-blind period	
	AXS-05 (n=295)	AXS-05 (n=83)	Placebo (n=84)
Age, years (SD)	74.0 (5.3)	73.3 (4.2)	74.2 (5.6)
Female, n (%)	186 (63.1)	54 (65.1)	51 (60.7)
Race, n (%)			
White	268 (90.8)	77 (92.8)	77 (91.7)
Black	26 (8.8)	5 (6.0)	7 (8.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Other or not reported	0 (0.0)	1 (1.2)	1 (0.6)
Baseline CMAI total score	73.3	44.3	45.4
Baseline MMSE score	19.3	21.1	21.7

CMAI = Cohen-Mansfield Agitation Inventory; MMSE = Mini-Mental State Examination

Statistically significant delay in the time to relapse of agitation

Primary endpoint (ACCORD-2): Time from randomization to relapse of AD agitation



Number at Risk

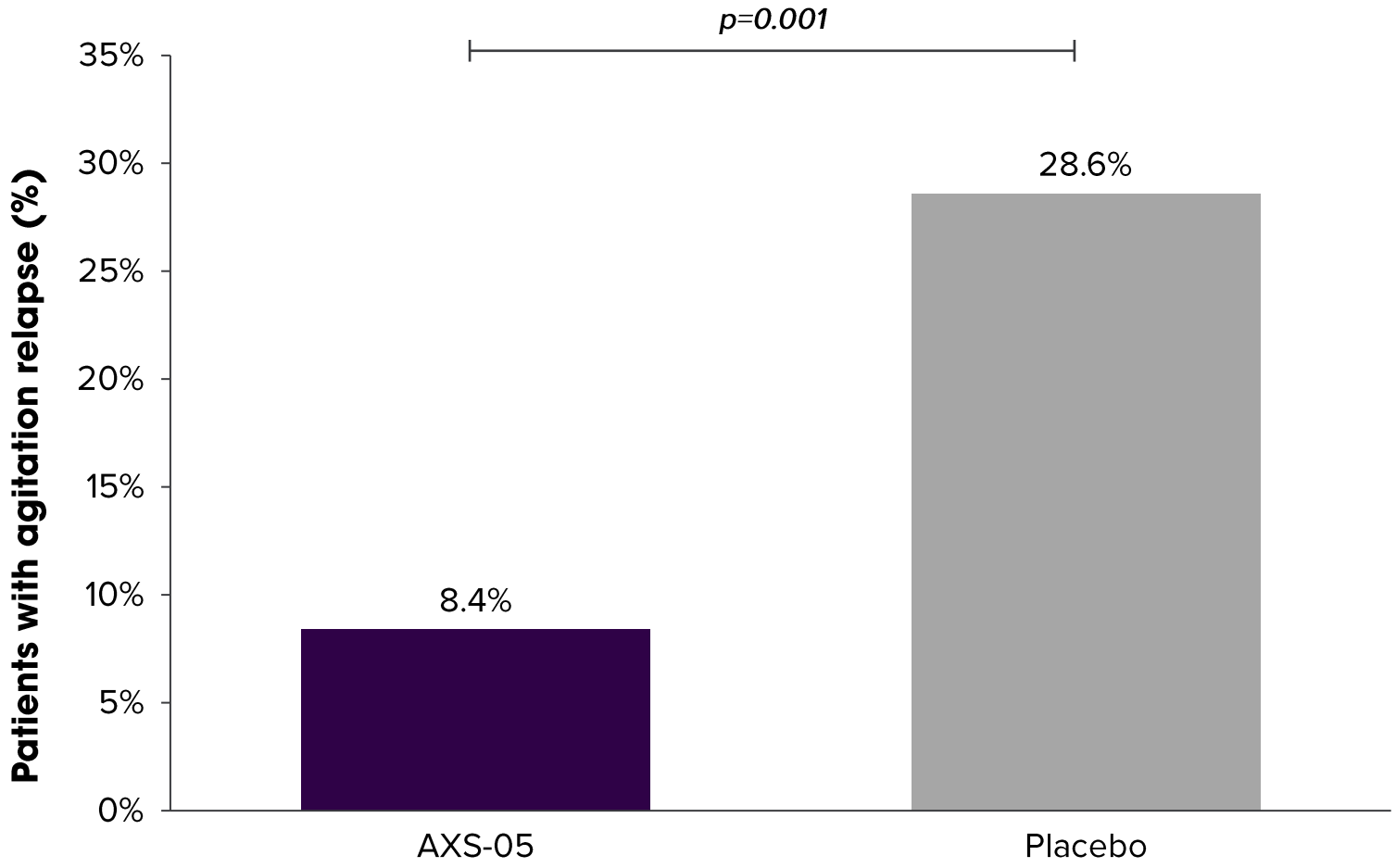
AXS-05	83	79	74	73	71	66	64	62	62	61	60	59	54	1
Placebo	84	82	77	74	71	65	56	52	51	47	45	43	39	0

Hazard Ratio for Time to Relapse	
Hazard Ratio (95% CI)	0.276 (0.119-0.641)
***p*-value**	0.001

AD = Alzheimer's disease

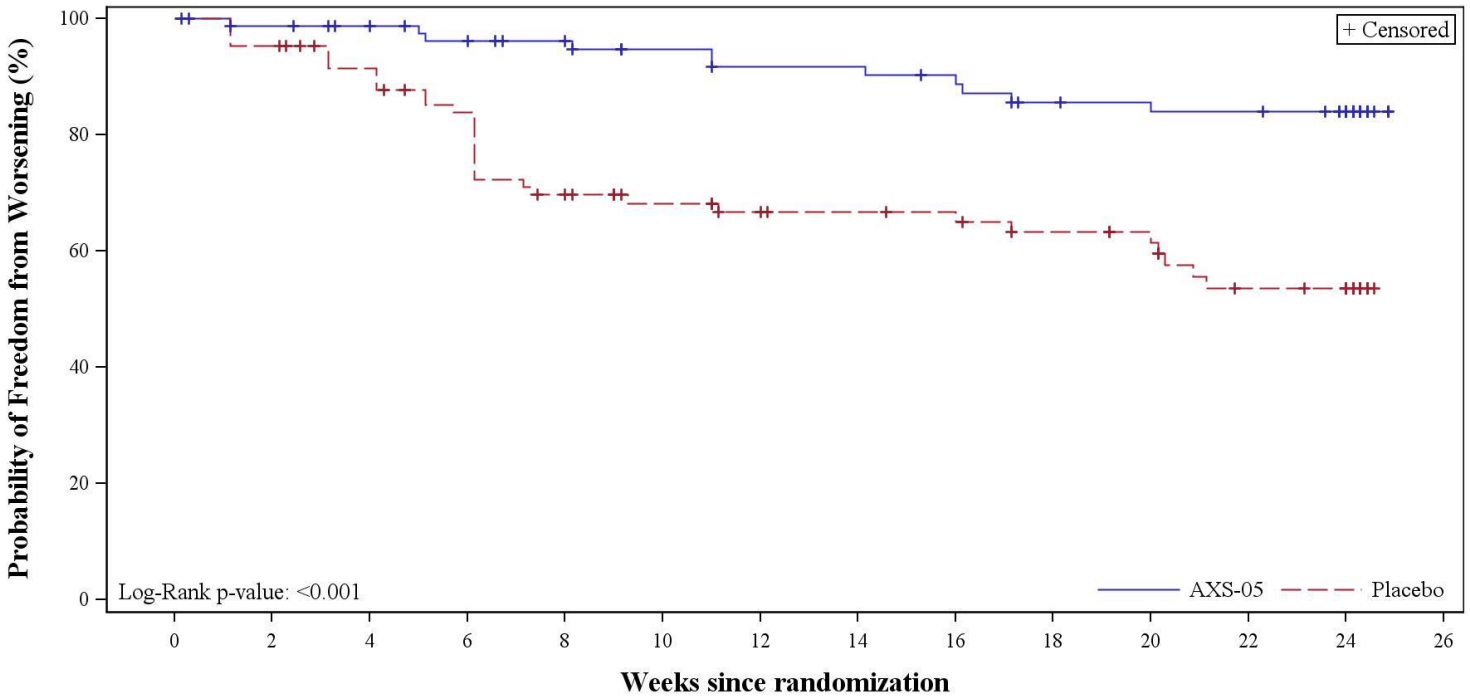
Statistically significant prevention of agitation relapse

Key secondary endpoint (ACCORD-2): Prevention of relapse of Alzheimer's disease agitation



Reduced worsening of overall Alzheimer's disease severity

ACCORD-2



Number at Risk

AXS-05	83	79	76	72	69	64	61	61	59	54	53	52	48	0
Placebo	84	80	73	65	53	47	43	41	40	36	34	26	25	0

Percent of patients with worsening AD severity (CGI-S Alzheimer's disease overall clinical status)		
AXS-05	**Placebo**	***p*-value**
13.3%	39.3%	<0.001

ACCORD-2 summary of adverse events

	Double-blind period	
Number of patients (%)	**AXS-05 (n=82)**	**Placebo (n=84)**
Incidence of TEAEs	24 (29.3)	27 (32.1)
Incidence of serious TEAEs	0 (0.0)	2 (2.4)
Discontinuation due to TEAEs	0 (0.0)	1 (1.2)
Most common TEAEs (≥3% in AXS-05 group)		
Anemia	3 (3.7)	1 (1.2)
Headache	3 (3.7)	2 (2.4)
Hyperkalemia	3 (3.7)	1 (1.2)
Somnolence	3 (3.7)	0 (0.0)
Back pain	3 (3.7)	0 (0.0)

- Falls reported in 2 patients (2.4%) in the AXS-05 group; only one deemed related to study medication
- No deaths reported in either treatment group
- AXS-05 was not associated with deaths, sedation, or cognitive decline as measured by the MMSE

TEAE = treatment emergent adverse event

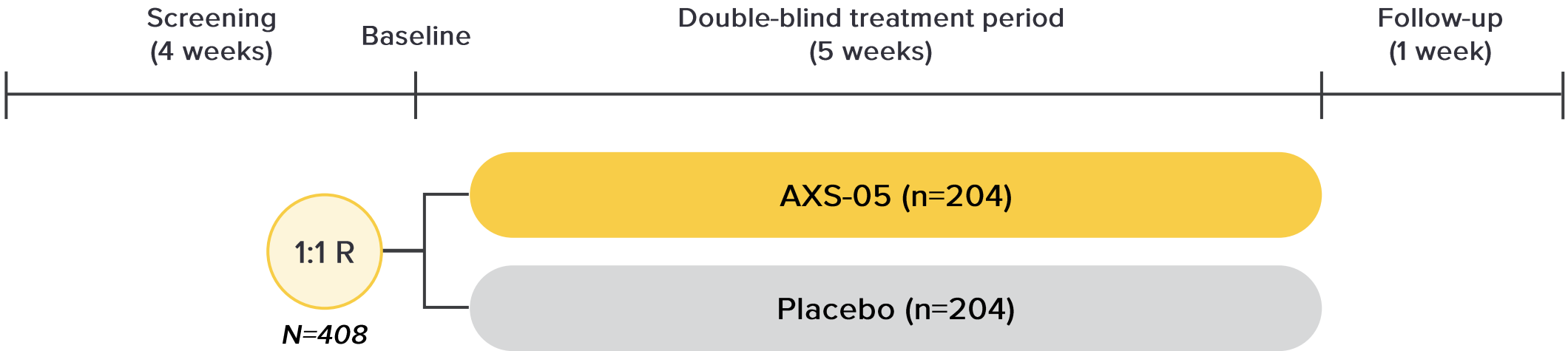
ADVANCE-2 Phase 3 trial topline results

ACCORD-1	ADVANCE-1†	ACCORD-2	ADVANCE-2	Long-term safety
Phase 3 (N=108)	*Phase 2/3 (N=366)*	*Phase 3 (N=167)*	*Phase 3 (N=408)*	*Phase 3 (N=456)*
• Efficacy and safety of AXS-05 vs. placebo • 9-week, open-label treatment period followed by 26-week, double-blind, multi-center, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Efficacy and safety of AXS-05 vs. placebo • Open-label treatment period followed by 24-week, double-blind, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Long-term efficacy and safety of AXS-05 • 12-month, open-label extension (OLE) of ACCORD-1 and ADVANCE-2

†Also established component contribution by demonstrating statistical superiority vs. bupropion

ADVANCE-2 trial design

Phase 3, multi-center, randomized, double-blind, placebo-controlled trial



Key eligibility criteria

- 65-90 years of age
- Diagnosis of probable AD (NIA-AA) and clinically significant agitation resulting from probable AD
- MMSE between 10 and 24
- NPI-AA score ≥4

Dose titration

- AXS-05 30 mg/105 mg once daily escalated up to 45 mg/105 mg twice daily

Primary endpoint

- Change from baseline in CMAI total score compared to placebo at Week 5

AD = Alzheimer's disease; NIA-AA = National Institute on Aging-Alzheimer's Association; MMSE = Mini-Mental State Examination; NPI-AA = Neuropsychiatric Inventory-Agitation/Aggression domain; CMAI = Cohen-Mansfield Agitation Inventory

ADVANCE-2 demographics and baseline characteristics

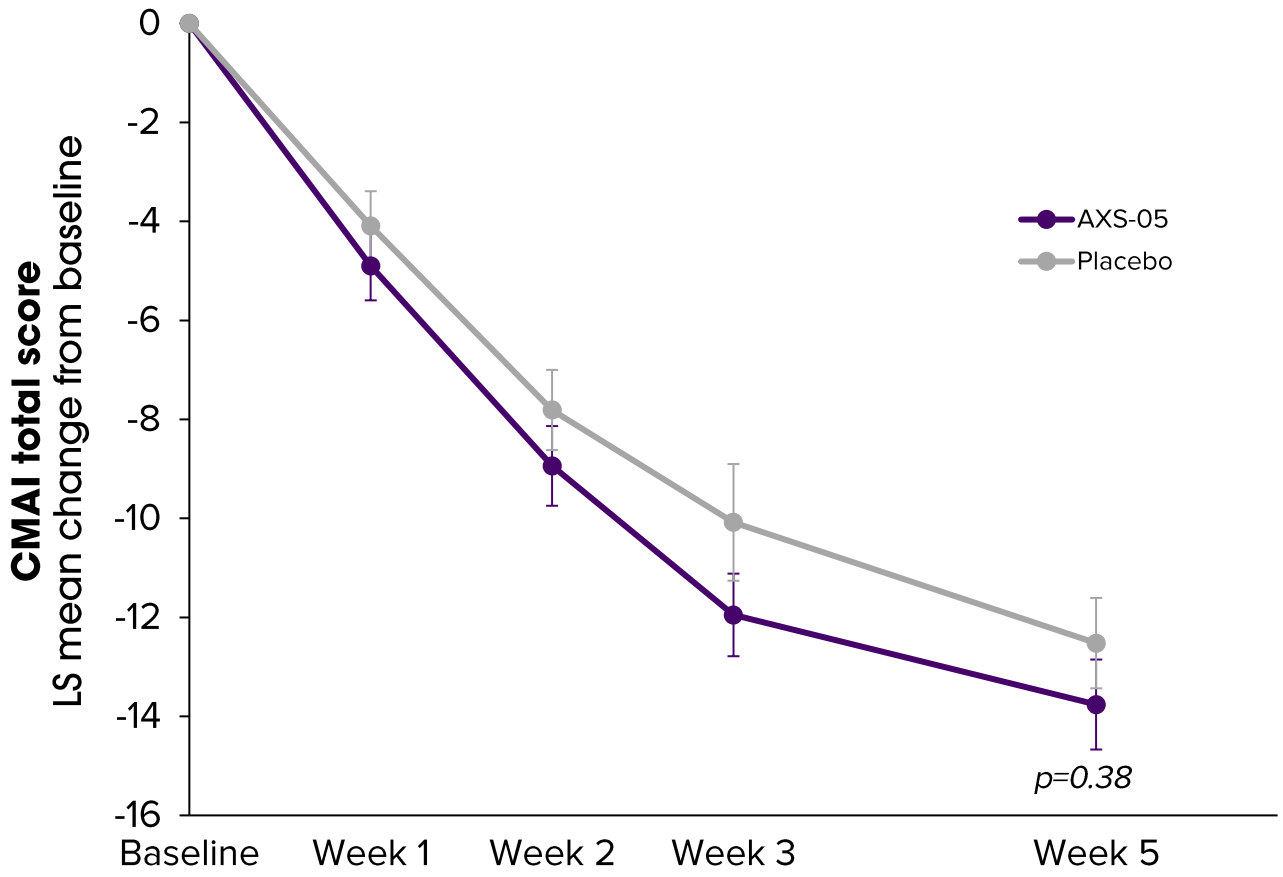
ITT population

	AXS-05 (n=204)	Placebo (n=204)
Age, years (SD)	73.6 (5.3)	75.0 (5.7)
Female, n (%)	130 (63.7)	112 (54.9)
Race, n (%)		
White	184 (90.2)	178 (87.3)
Black	18 (8.8)	23 (11.3)
Asian	2 (1.0)	2 (1.0)
Other or not reported	0 (0.0)	1 (0.5)
Baseline CMAI total score	71.0	73.5
Baseline MMSE score	19.2	19.1

CMAI = Cohen-Mansfield Agitation Inventory; MMSE = Mini-Mental State Examination

Improvement in symptoms of agitation

Primary endpoint (ADVANCE-2): Change from baseline in CMAI total score at Week 5



Numerically greater improvement in the CMAI total score vs. placebo demonstrated at all timepoints throughout the trial

Secondary endpoints numerically favored AXS-05 over placebo, consistent with the primary endpoint

CMAI = Cohen-Mansfield Agitation Inventory

ADVANCE-2 summary of adverse events

Safety population

Number of patients (%)	AXS-05 (n=204)	Placebo (n=204)
Incidence of TEAEs	53 (26.0)	44 (21.6)
Incidence of serious TEAEs	2 (1.0)	0 (0.0)
Discontinuation due to TEAEs	3 (1.5)	0 (0.0)
Most common TEAEs (≥3% in AXS-05 group)		
Dizziness	12 (5.9)	3 (1.5)
Headache	9 (4.4)	7 (3.4)

- Falls reported in one patient (0.5%) in each treatment arm, which was deemed unrelated to study medication in the AXS-05 group
- No deaths reported in either treatment group
- AXS-05 was not associated with death, sedation, or cognitive decline as measured by the MMSE

TEAE = treatment emergent adverse event

Long-term safety trial topline results

ACCORD-1	ADVANCE-1†	ACCORD-2	ADVANCE-2	Long-term safety
Phase 3 (N=108)	*Phase 2/3 (N=366)*	*Phase 3 (N=167)*	*Phase 3 (N=408)*	*Phase 3 (N=456)*
• Efficacy and safety of AXS-05 vs. placebo • 9-week, open-label treatment period followed by 26-week, double-blind, multi-center, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Efficacy and safety of AXS-05 vs. placebo • Open-label treatment period followed by 24-week, double-blind, placebo-controlled, randomized withdrawal period	• Efficacy and safety of AXS-05 vs. placebo • 5-week, randomized, double-blind, placebo-controlled, multi-center, parallel-group trial	• Long-term efficacy and safety of AXS-05 • 12-month, open-label extension (OLE) of ACCORD-1 and ADVANCE-2

†Also established component contribution by demonstrating statistical superiority vs. bupropion

Long-term safety trial summary of adverse events

Number of patients (%)	AXS-05 (n=456)
Incidence of TEAEs	182 (39.9)
Incidence of serious TEAEs	12 (2.6)
Discontinuation due to TEAEs	2 (0.4)
Most common TEAEs (≥3%)	
Headache	25 (5.5)
Diarrhea	15 (3.3)
Dizziness postural	14 (3.1)
Fall	14 (3.1)
Hyperkalemia	14 (3.1)
Somnolence	14 (3.1)
Urinary tract infection	14 (3.1)

- Falls reported in 3.1% of patients, with only 0.2% deemed related to study medication
- No deaths occurred in the trial
- None of the serious TEAEs were deemed related to study drug
- AXS-05 was not associated with death, sedation, or cognitive decline as measured by the MMSE

TEAE = treatment emergent adverse event

Four Phase 3 trials support efficacy and safety of AXS-05 in Alzheimer's disease agitation

ADVANCE-1	ADVANCE-2	ACCORD-1	ACCORD-2
Randomized, double-blind, active & placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized withdrawal, double-blind, placebo-controlled	Randomized withdrawal, double-blind, placebo-controlled
45 mg/105 mg twice daily	45 mg/105 mg twice daily	45 mg/105 mg twice daily	45 mg/105 mg twice daily
5 weeks	5 weeks	Up to 26 weeks	Up to 24 weeks
N=366	*N=408*	*N=108*	*N=167*
Primary endpoint: Mean reduction from baseline in CMAI total score at Week 5 of 15.4 points for AXS-05 and 11.5 points for placebo (p=0.010)	Primary endpoint: Mean reduction from baseline in CMAI total score at Week 5 of 13.8 points for AXS-05 and 12.6 points for placebo (p=0.380)	Primary endpoint: Time to relapse: hazard ratio of 0.275 (p=0.014)	Primary endpoint: Time to relapse: hazard ratio of 0.276 (p=0.001)

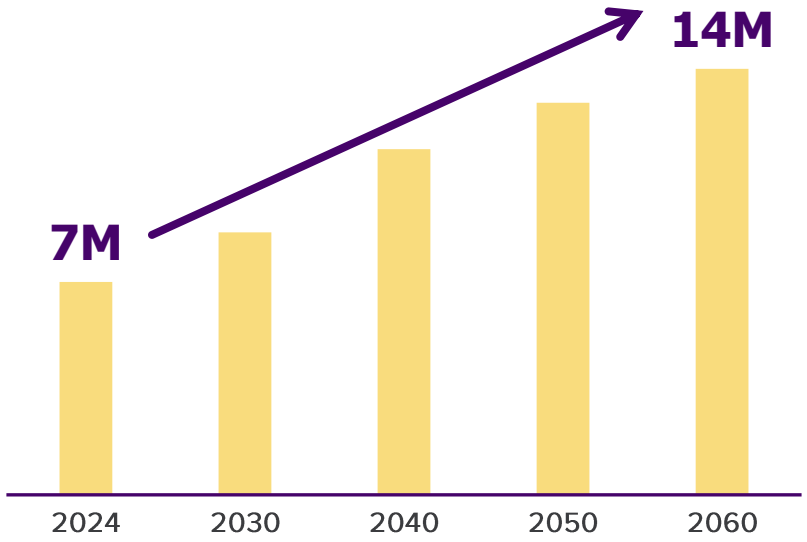
Alzheimer's disease agitation

Sue Giordano, PhD

Vice President of Medical Affairs

Alzheimer's disease (AD) agitation

Number of U.S. adults aged 65+ with Alzheimer's dementia expected to double by 2060[1]



Alzheimer's disease (AD) is the most common form of dementia, affecting approximately ***7M*** people in the U.S.[1]

Agitation is reported in ***~70%*** of people with AD and is characterized by emotional distress, verbal and physical aggressiveness, disruptive irritability, and disinhibition[1,2]

Psychosocial interventions of AD agitation, while recommended as first line treatment, are not always effective[3]

1. Alzheimer's Association (2024); 2. Trachtenberg et al. *J Neuropsychiatry Clin Neurosci.* (2002); 3. Porsteinsson, A.P. & Antonsdottir, I.M. *Expert Opin Pharmacother.* (2017)

The four IPA criteria for agitation in cognitive disorders[1]

Cognitive impairment or dementia syndrome

- Patient meets criteria for a cognitive impairment or dementia syndrome, including:
  - Alzheimer's disease
  - Mild cognitive impairment
  - Other dementias

Agitation behavior and duration

- ≥1 agitation behavior associated with emotional distress
- Behavior is persistent, frequently recurring for ≥2 weeks, or represents a change form the patient's usual behavior

Agitation behavior severity

- Behavior(s) is severe and associated with excess distress or produces excess disability beyond that due to cognitive impairment
- Significantly impairs ≥1 of the following:
  - Interpersonal relationships
  - Other aspects of social functioning
  - Ability to perform or participate in daily activities

Cause of agitation behavior

- Agitation is not attributable to:
  - Another psychiatric disorder or medical condition
  - Suboptimal care conditions
  - Physiological effects of a substance

1. Cummings, J., et al. *Int Psychogeriatr.* (2015)
IPA = International Psychogeriatric Association

Agitation is a common behavioral symptom that may present in ~70% of patients with Alzheimer's disease[1,2]

Agitation encompasses three broadly defined symptom domains including both non-aggressive and aggressive behaviors[3,4]

1. Alzheimer's Association (2024); 2. Tractenberg, R.E. et al. *J Neuropsychiatry Clin Neurosci.* (2002); 3. Cummings, J., et al. *Int Psychogeriatr.* (2015); Sano, M., et al. *Int Psychogeriatr.* (2023)

Agitation worsens impact of Alzheimer's disease and adds significant burden on patient and caregiver

Agitation in patients with Alzheimer's disease is associated with[1-3]:

Accelerated disease progression and cognitive decline

Earlier institutionalization

Increased mortality risk

Greater health care utilization

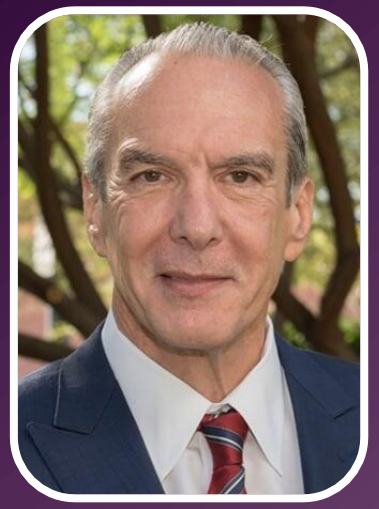
Increased caregiver burden

Higher concomitant medication use

Poor quality of life

1. Porsteinsson, A.P. & Antonsdottir, I.M. *Expert Opin Pharmacother.* (2017); 2. Fillit, H., et al. *Int J Geriatr Psychiatry* (2021); 3. Jones, E., et al. *J Alzheimers Dis.* (2021)

Clinical perspective



Dr. Jeffrey Cummings, MD, ScD

Vice Chair of Research, UNLV Department of Brain Health

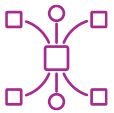
Unmet need in the treatment of Agitation associated with Alzheimer's disease

- Agitation affects the majority of patients with Alzheimer's disease and is one of the most troubling and consequential aspects of Alzheimer's disease for patients and caregivers.
- Current pharmacologic treatments are primarily off-label medications:
  - Typical and atypical antipsychotics, benzodiazepines, antiepileptics, antidepressants
- Limitations of off-label medications:
  - Sedation, extrapyramidal side effects, falls, worsening of cognition, cardiovascular and cerebrovascular events
  - Modest efficacy
- Only 1 FDA-approved agent, an atypical antipsychotic
- There is an urgent unmet need for new effective pharmacological treatments with favorable safety and tolerability

Challenges for clinical trials of agents for the treatment of neuropsychiatric syndromes

Multiple specific challenges

- Robust placebo-group improvement:
  - True placebo response
  - Caregiver placebo response
  - Trial and clinician response
- Issues with scales and raters
- Disease complexity and natural history of agitation



Benefits of randomized withdrawal trials

- Mitigates against placebo response:
  - All subjects treated with active therapy
  - Responders randomly assigned to active or placebo
- Assesses rate or time to symptom response, maintenance of effect
- Type 1 error control in conjunction with parallel group trial

1. Zhu, 2021. Front. Psychiatry 11:562660. 2. Dowden and Munro J. Nat Rev Drug Discov. 2019 Jul;18(7):495-496. 3. Wong, Siah, and Lo. Biostatistics. 2019 Apr 1;20(2):273-286. 4. Hopkins et al. Current Medical Research and Opinion, 39:3, 467-471

Perspective on AXS-05 in Alzheimer's disease agitation

Comprehensive Phase 3 clinical program

- Four controlled Phase 3 clinical trials evaluated AXS-05 in Alzheimer's disease agitation
- Two distinct trial paradigms (parallel group and randomized withdrawal) is a strength
- Program evaluated both induction and maintenance effects of therapy

Efficacy of AXS-05 in Alzheimer's disease agitation

- Strong statistically significant and clinically meaningful efficacy demonstrated in ADVANCE-1, ACCORD-1, and ACCORD-2
- Global improvement in Alzheimer's disease severity observed

Safety of AXS-05 in Alzheimer's disease agitation

- Well tolerated across controlled and long-term studies
- ADVANCE-2 provides supportive controlled safety data
- No association with death, increased risk of falls, sedation, or cognitive decline observed

Q&A